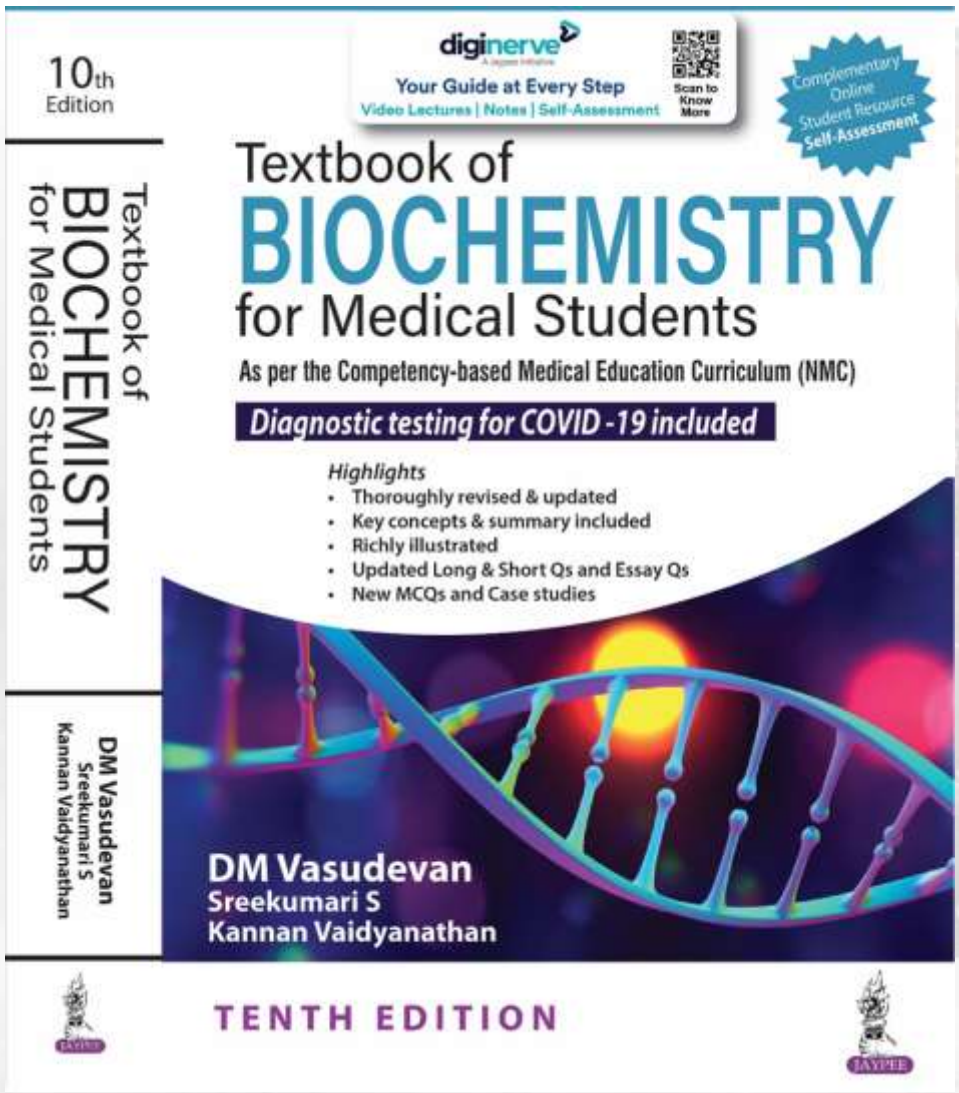
Chapter 42:

Biochemistry of Cancer



Textbook of

BIOCHEMISTRY

for Medical Students

By DM Vasudevan, *et al.*

TENTH EDITION

Etiology of Cancer

All cancers are multifactorial in origin. They include genetic, hormonal, metabolic, physical, chemical, and environmental factors. Most human cancers are spontaneous.

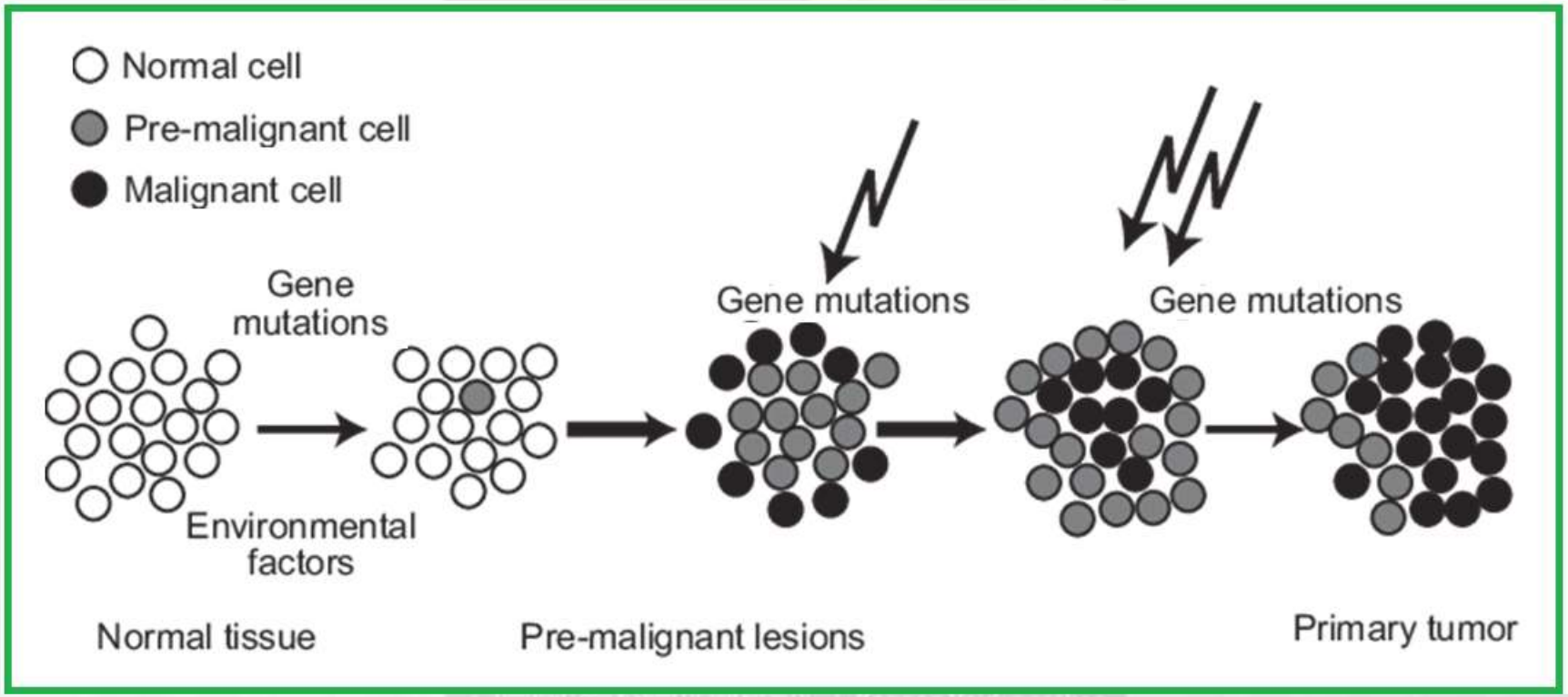
All cancers originate usually from one aberrant cell, which goes on to multiply and produce a tumor mass. Thanks to the surveillance by the immune system, these aberrant cells are usually destroyed.

As age advances, the number of mutations accumulate, hence the statistical probability of the incidence of cancer is increased. No wonder, cancer is a disease of old age, especially after 60 years.

Mutagens

Any substance which increases the rate of mutation can also enhance the rate of incidence of cancer. Therefore, all carcinogens are mutagens. Examples are X-ray, gamma ray, ultraviolet ray.

Some human cancers are caused by chemicals. These may be introduced into the body (a) occupation (aniline, asbestos), (b) diet (aflatoxins) or (c) lifestyle (smoking). Chemical carcinogens act cumulatively. Tobacco, food additives, coloring agents, and aflatoxins are common carcinogens in our environment.



Successive mutations lead to cancer.

Some chemical carcinogens

Polycyclic aromatic hydrocarbons	Benzopyrenes, Cholanthrenes, Dimethyl benzanthracene (DMBA)
Aromatic amines	N-Methyl-4-aminoazobenzene (MAB)
Nitroso compounds	Dimethyl nitrosamine
Natural compounds	Aflatoxins

Aflatoxins

They are a group of chemically related compounds synthesized by the fungi, *Aspergillus flavus*. The mould grows on rice, wheat and groundnut, when kept in damp conditions. The fungi may grow in cattle fodder, which may enter into the human body through the cow's milk. Aflatoxins are powerful carcinogens, which produce hepatomas.

Cigarette

Lung cancer is associated with the habit of cigarette smoking. Cigarette contains many carcinogens, the most important group being benzopyrenes. Other important deleterious substances in cigarette smoke are nicotine, carbon monoxide, nitrogen dioxide and carbon soot.

The incidence of lung cancer is increased to 15 times more in persons smoking 10 cigarettes per day. Moreover, nonsmoking spouse of a heavy smoker will have 5 times more probability to get lung cancer than a nonsmoker. This effect is called **"passive smoking"**.

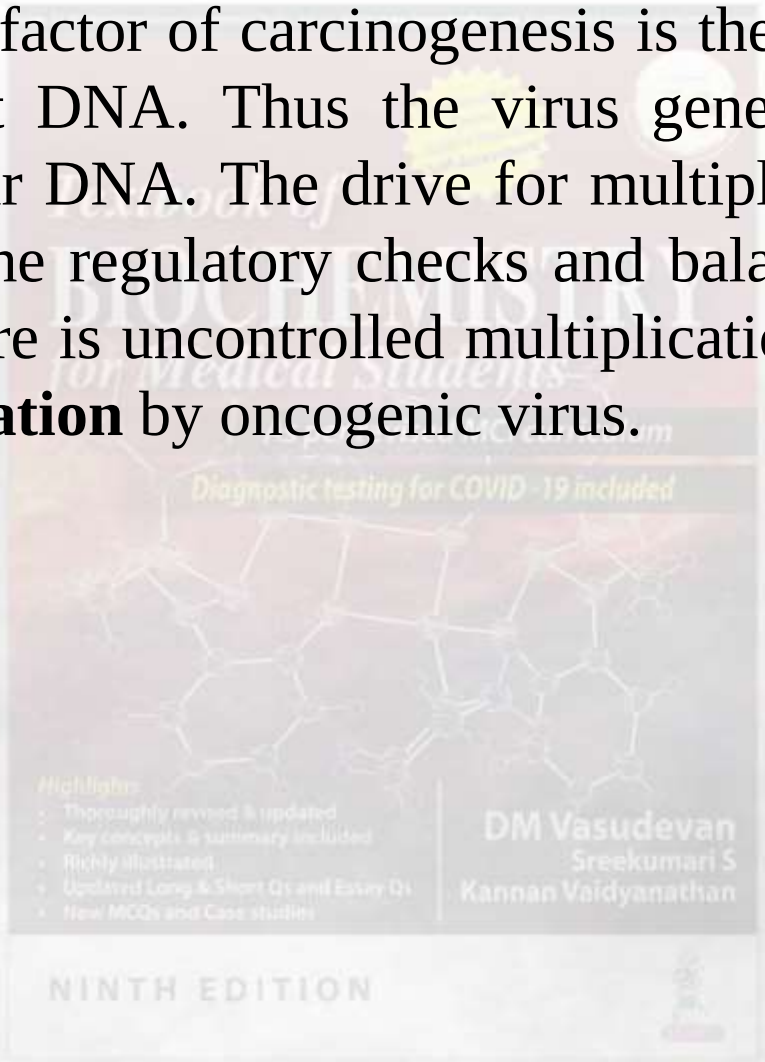
Oral cancer is strongly associated with chewing of **tobacco**.

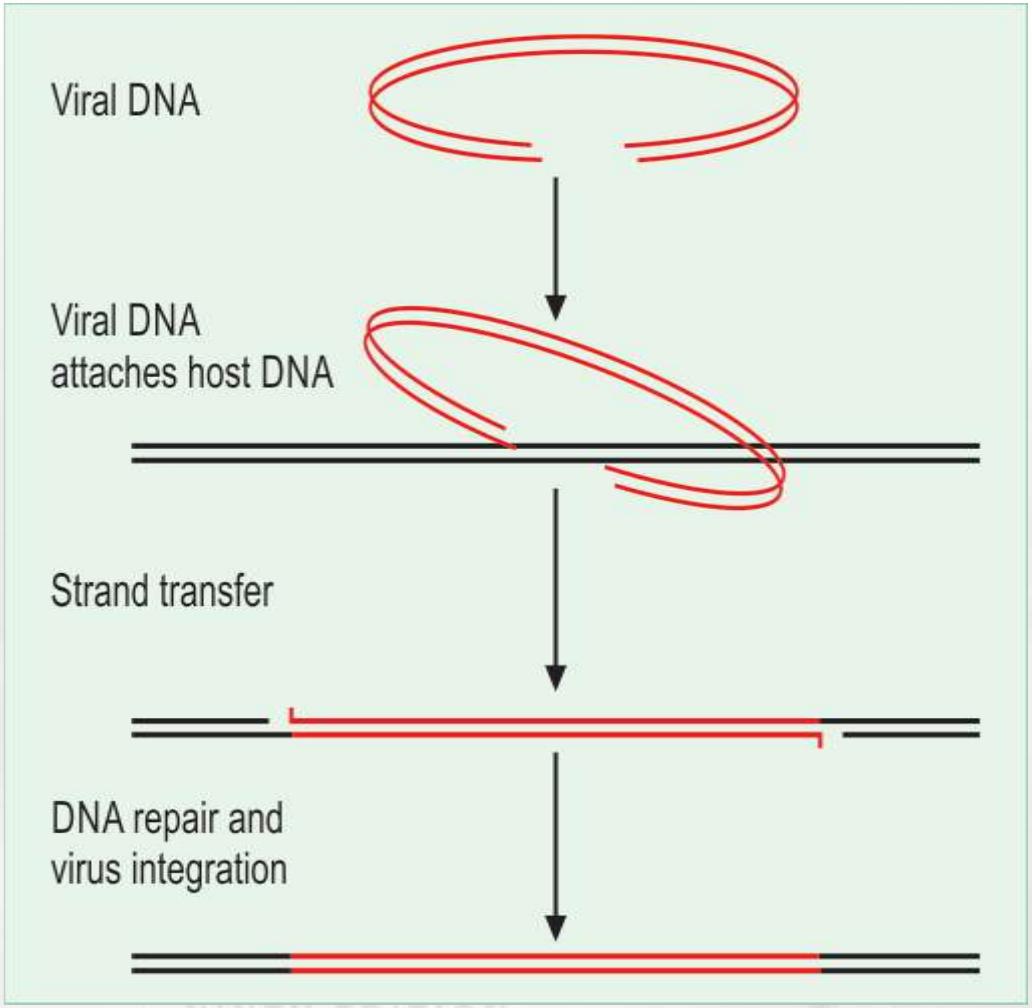
Antimutagens

- These are substances which will interfere with tumor promotion.
- **Vitamin A** and carotenoids are shown to reverse precancerous conditions.
- **Vitamin E** acts as an antioxidant, preventing the damage made by free radicals and superoxides.
- **Vitamin C** prevented the production of new cancer cases in aniline workers.
- **Curcumin** in turmeric, is known to prevent mutations.
- Fibre content of diet is beneficial to decrease colon cancers.
- **Flavonoids** possess antimutagenic properties.
- **Phenolic** compounds found in fruits like grapes, strawberries, walnuts, etc. are found to be antimutagenic.

Oncogenic Viruses

Another etiological factor of carcinogenesis is the integration of viral genes into the host DNA. Thus the virus genes become part and parcel of the cellular DNA. The drive for multiplication by the virus genome overrules the regulatory checks and balances of the cellular mechanism. So, there is uncontrolled multiplication of the cells. This is called **transformation** by oncogenic virus.





Virus integrated into the host DNA.

Viruses producing tumors in animals

Virus	Nucleic acid of virus	Host	Type of tumor produced
Papova virus group			
SV-40	DNA	Mouse	Sarcoma
Papilloma	DNA	Rabbit	Papilloma
Marek	DNA	Chicken	Lymphoma
Retrovirus type C			
Gross	RNA	Mouse	Leukemia,
Rous	RNA	Avian	Sarcoma
Retrovirus type B			
Bittner	RNA	Mouse	Mammary tumor

Viruses associated with human cancers

Virus	Abbreviation	Associated human disease
Epstein-Barr virus	EBV	Burkitt's lymphoma (BL); Nasopharyngeal carcinoma (NPC)
Human papilloma virus	HPV	Uterine cervical carcinoma
Hepatitis B virus	HBV	Hepatoma

Burkitt's Lymphoma

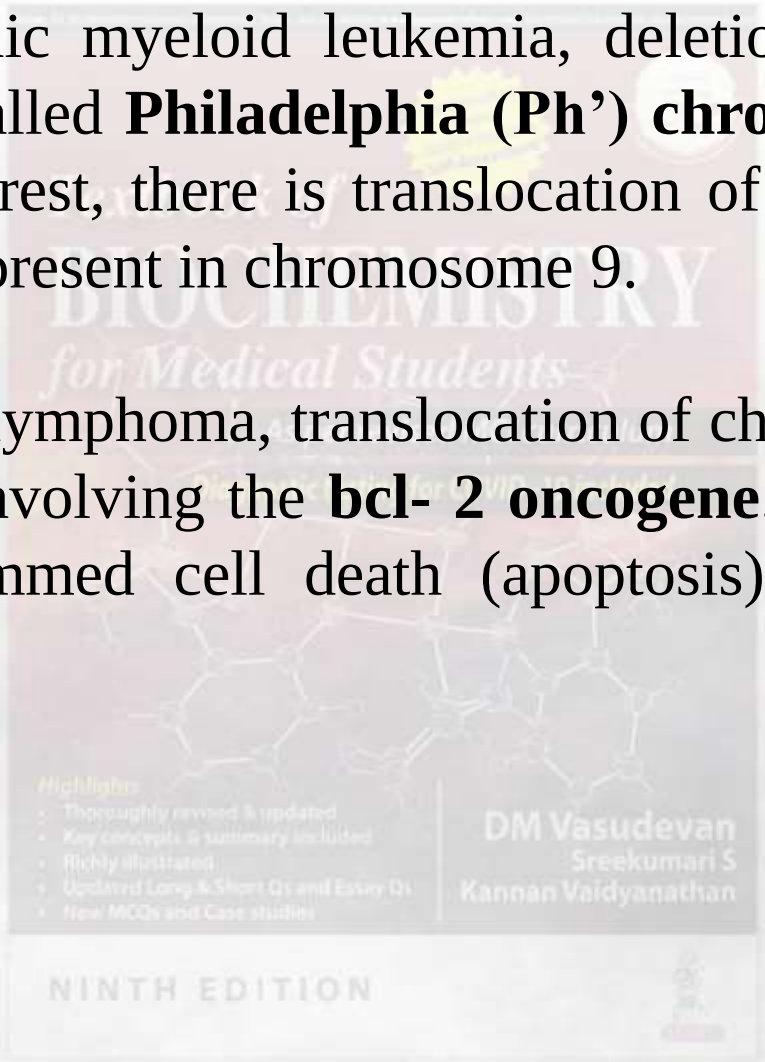
Burkitt's lymphoma (BL) is caused by the **Epstein-Barr (EB) virus.** The lymphoma progression is through 3 different events. The first step is **infection** with EBV which specifically infects B lymphocytes. The B cells are now immortalized, that is, they can be cultured indefinitely in artificial medium. But they are still dependent on the B-cell growth factor (BCGF) for proliferation.

The second step is the **chromosome translocation**, usually from chromosome 8 to 14, but sometimes from 8 to 2 or from 8 to 22. The chromosome 14 contains gene for immunoglobulin heavy chain, 2 contains gene for kappa light chain and 22 for lambda light chain. The transposing region in chromosome 8 contains the oncogene c-myc. This transposition of oncogenes confers BCGF-independence; but these B cells can grow very slowly.

The third step is the activation of **c-myc oncogene**, with consequent malignancy.

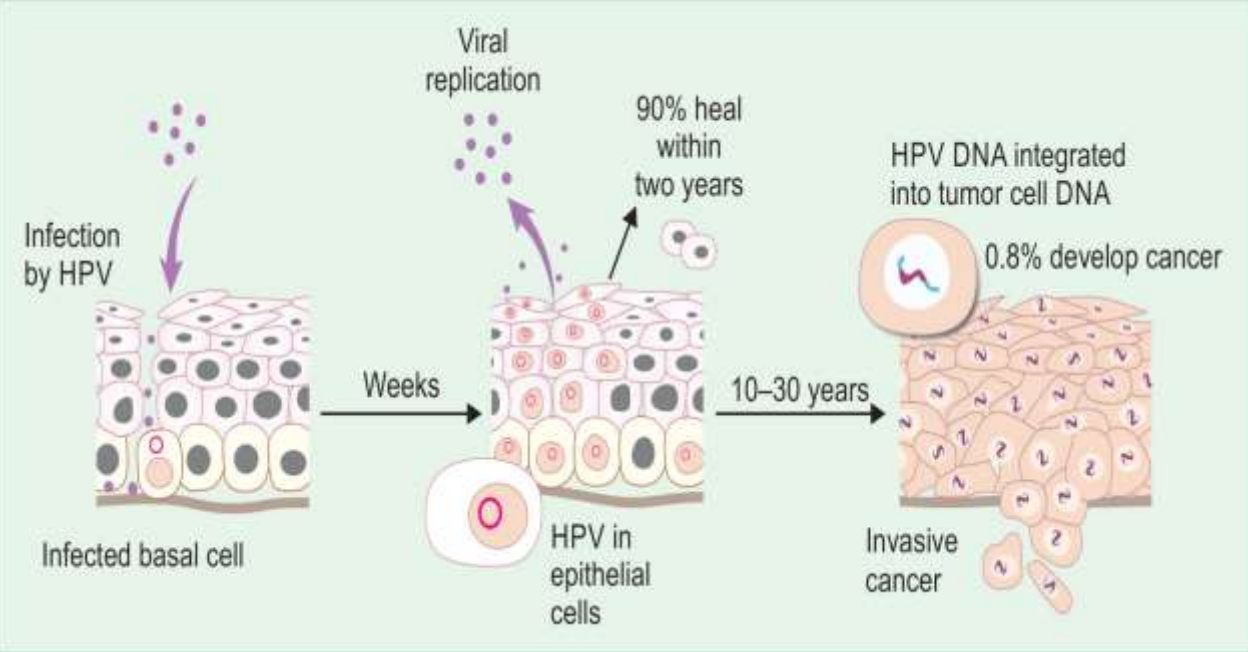
Similarly, in chronic myeloid leukemia, deletion of short arm of chromosome 22, called **Philadelphia (Ph') chromosome** is seen in 80% cases. In the rest, there is translocation of 9 to 22 leading to activation of c-abl present in chromosome 9.

In Non-Hodgkin's lymphoma, translocation of chromosome 14 to 18 is very common, involving the **bcl- 2 oncogene**. The bcl-2 product suppresses programmed cell death (apoptosis) leading to tumor formation.



Human Papilloma Virus (HPV)

- HPV types 16 and 18 are associated with human uterine cervical cancer; they cause 70% of all cervical cancers. HPV DNA has been shown in the cancer cells. HPV is integrated into the host DNA of human cervical cancer cells.
- The HPV infects epithelial cells in the cervical mucosa; the virus multiplies and lyses the host cells, causing a lesion. In 99% of such cases healing occurs within 6 months to 2 years. But in about 1% cases, the HPV DNA is integrated into some of the host cells. After about 10–30 years, these cells develop into invasive cancer.
- Vaccines against high risk HPV16 and 18 types are now developed that provide 95% protection from developing cervical cancer.



Human papilloma virus (HPV) and host interaction. Left slide, HPV infects one cell in the basal layer in human uterine cervix. In the middle slide, within few weeks, the HPV spreads to most of the cells; replicates, and a lesion is manifested. Some host cells will escape the infection. In 99% cases, the lesion subsides within 6 months to 2 years' time. In the right slide, in 1% cases, the virus is integrated into the host DNA, and remains dormant. After 10–30 years, cancer is developed. Here malignant cells are shown to break the basal layer and invade into surrounding tissues.

Oncogenes

Oncogenes are the genes capable of causing cancer. In Rous sarcoma virus, the full virus produces sarcoma in avians but a strain of virus deficient in a particular gene could not cause the disease. Hence this gene was named as sarcoma gene, abbreviated as src.

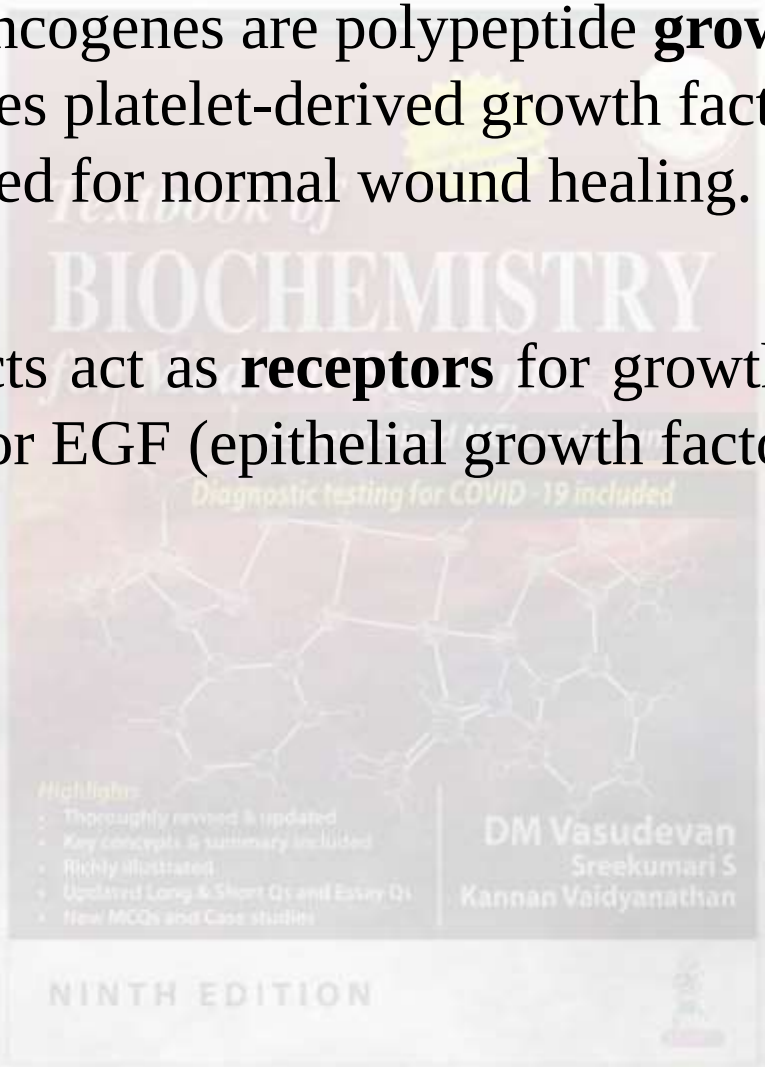
However, the same DNA sequences are available in normal avian cells also. To distinguish these two genes, they are denoted as **V-src** (viral gene) and **C-src** (cellular gene). The oncogenes present in normal cells are also called as **proto-oncogenes**. Today, more than 100 human proto-oncogenes are known.

Proto-oncogenes are important regulatory genes of the cells.

Proto-oncogenes are Regulatory Genes

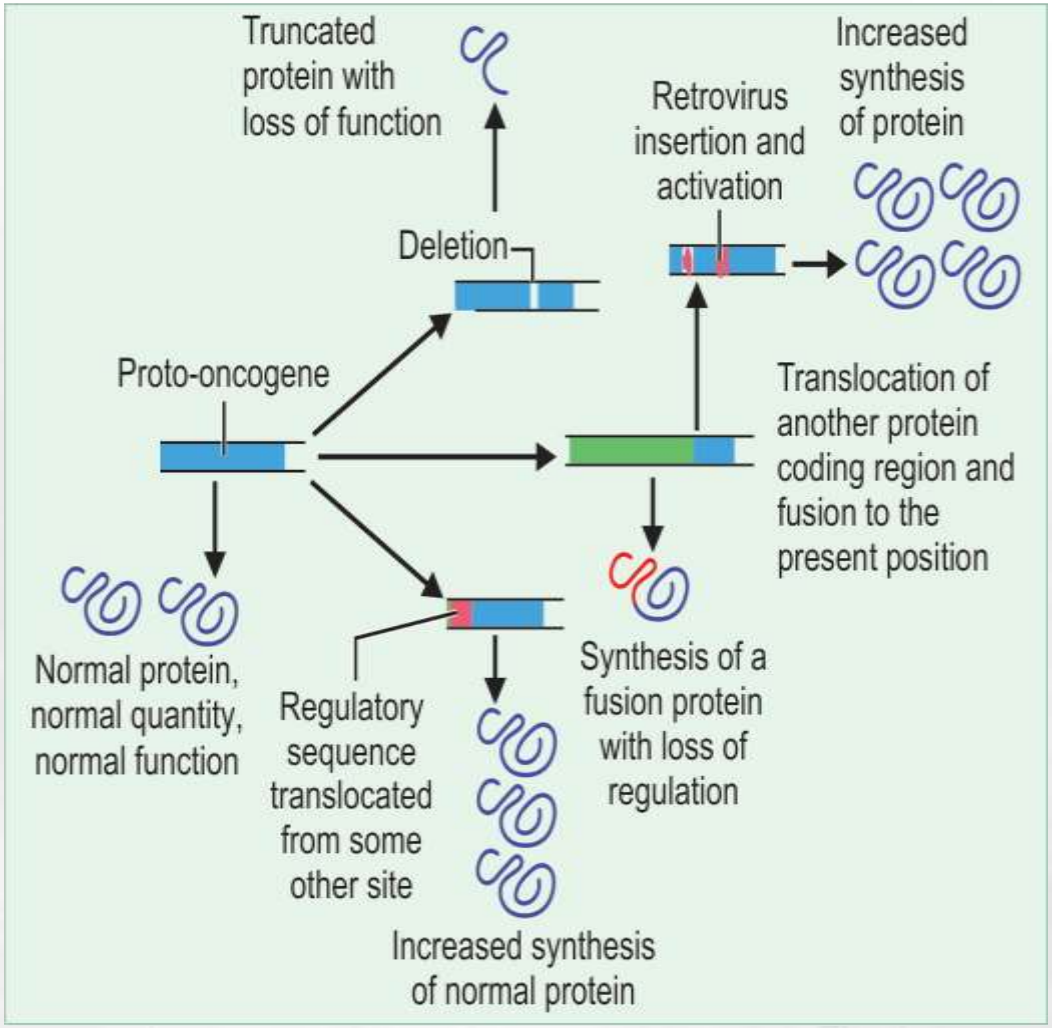
Products of many oncogenes are polypeptide **growth factors**, e.g. *sis* gene produces platelet-derived growth factor (PDGF). This factor is required for normal wound healing.

Some of the products act as **receptors** for growth factor, e.g. erb-B produces receptor for EGF (epithelial growth factor)

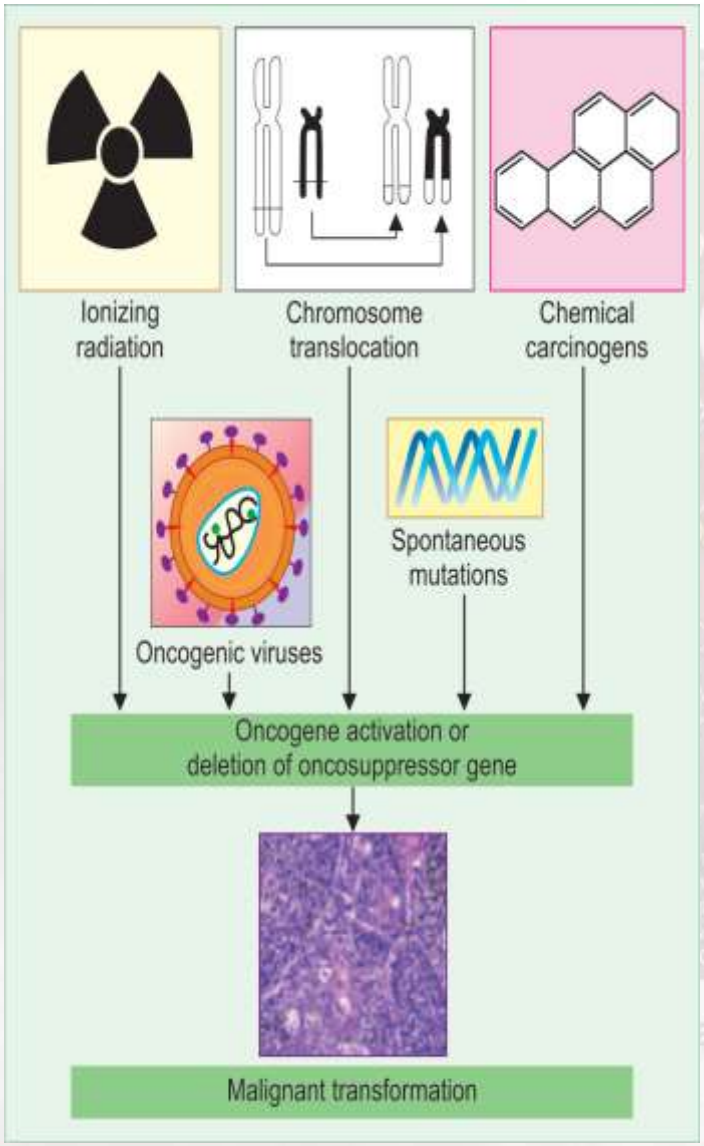


Some cellular oncogenes

Oncogene	Virus carrying the gene	Oncogene product	Subcellular localisation of the oncogene product
Abl	Abelson leukemia virus in mouse	Tyrosine kinase	Plasma Membrane
erb-B	Erythroblastosis virus in chicken	Receptor for epidermal growth factor (EGFR)	Membrane
Myc	Myelocytoma virus in chicken	DNA-binding protein	Nucleus
sis	Simian sarcoma virus in monkey	Platelet derived growth factor (PDGF)	Membrane
Ras	Rat Sarcoma	GTPase	Cytoplasm



Proto-oncogene activation by various means.



Unified concept of carcinogenesis. Many Factors activate oncogenes. Viruses, chemical carcinogens, chromosome translocations, gamma rays, spontaneous mutations, may converge into one biochemical abnormality, that is, the activation of oncogenes leading to malignancy.

Oncosuppressor Genes

These are the genes, which normally protect the individual from developing a cancer. When the gene is deleted or mutated, cancer results. The oncosuppressor gene, **p53** is the gene encodes a **phosphoprotein** with molecular weight 53,000. It blocks the cells that have damaged DNA by triggering the blocking of cell division until the damage is repaired. If the DNA damage is severe, the p53 directs the cell to commit suicide by triggering apoptosis. Most tumors have a complete absence of p53, whereas others show mutant nonfunctional p53. Normal p53 can suppress transformation ability of oncogenic viruses in vitro. It is also seen that p53 activates the expression of genes that suppress cell proliferation.

Similarly the ***RB* gene** encodes a protein designated as p105 (Molecular weight:105,000). This protein is found to suppress cell proliferation, and to prevent the activity of various oncogenes. Only when both alleles of the *RB* gene are deleted (homozygous), the retinoblastoma results.

***BRCA* gene mutations**: A blood test is done for women who are likely to have BRCA mutations (those with a family history of breast cancer). Mutations are seen in 5% of breast cancers and 10–15% of ovarian cancers and more than 50% of patients with positive family history of breast or ovarian cancer.

Important oncosuppressor genes

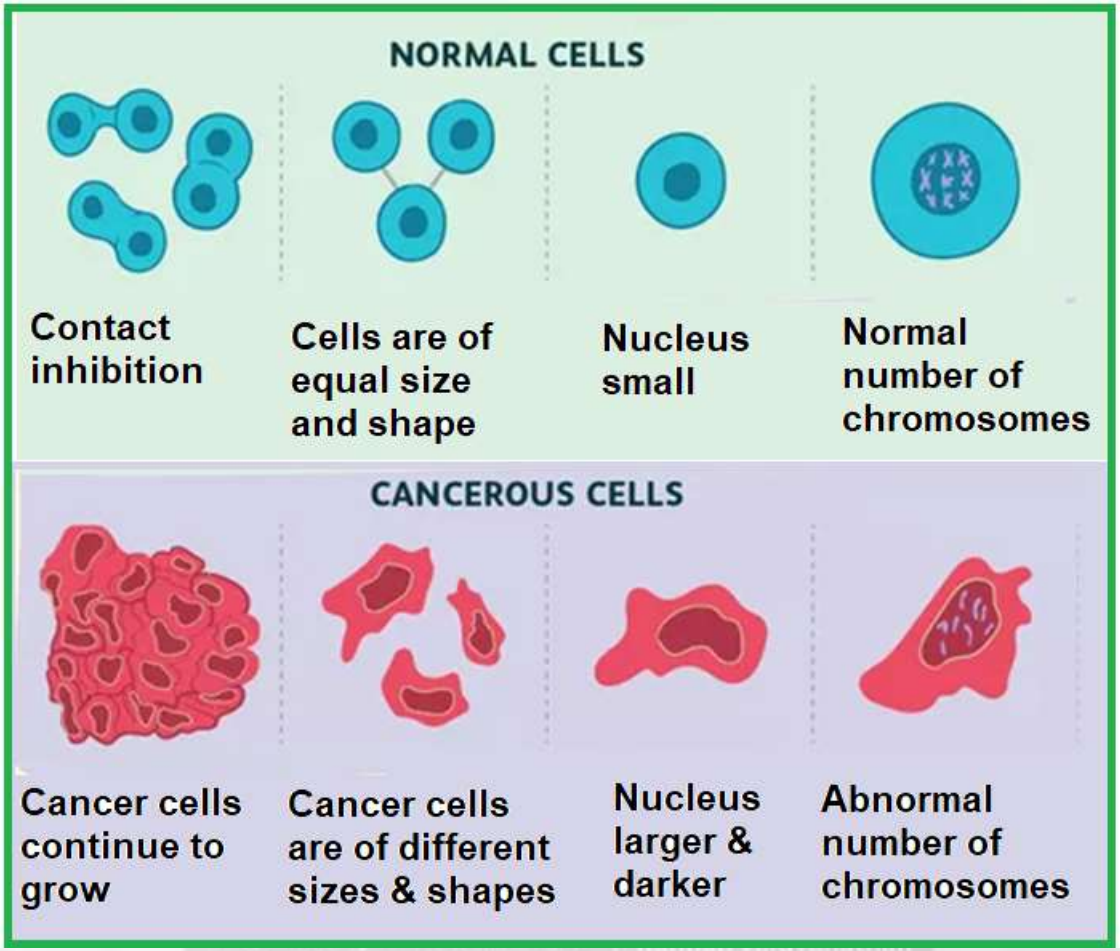
Name of the oncosuppressor	Abbreviation
Retinoblastoma	RB
Wilms' tumor	WT
Familial adenomatous polyposis	FAP
Deleted in colon cancer	DCC
Gene for protein-53	p53
Familial breast cancer	BRCA

Some important growth factors

Growth factor	Abbre-viation	Produced by location	Function
Epidermal growth factor	EGF	Fibroblasts, submaxillary gland	Stimulates epidermal and epithelial cells
Transforming growth factor-beta	TGF-beta	Platelets, placenta	Inhibition of fibroblasts
Platelet derived growth factor	PDGF	Platelets	Accelerates wound healing
Nerve growth factor	NGF	Submaxillary gland	Growth of sensory neurons

Some important growth factors, continued

Growth factor	Abbre-viation	Produced by location	Function
Erythropoietin	EP	Kidney	Stimulates erythropoiesis
Granulocyte colony stimulating factor	GCSF	Endothelial cells, and fibroblasts	Stimulates granulocytes
Monocyte colony stimulating factor	MCSF	Endothelial cells	Stimulates monocytes
Tumor necrosis factor alpha	TNF-alpha	Monocyte	Necrosis of tumor cells, proliferation of leukocytes

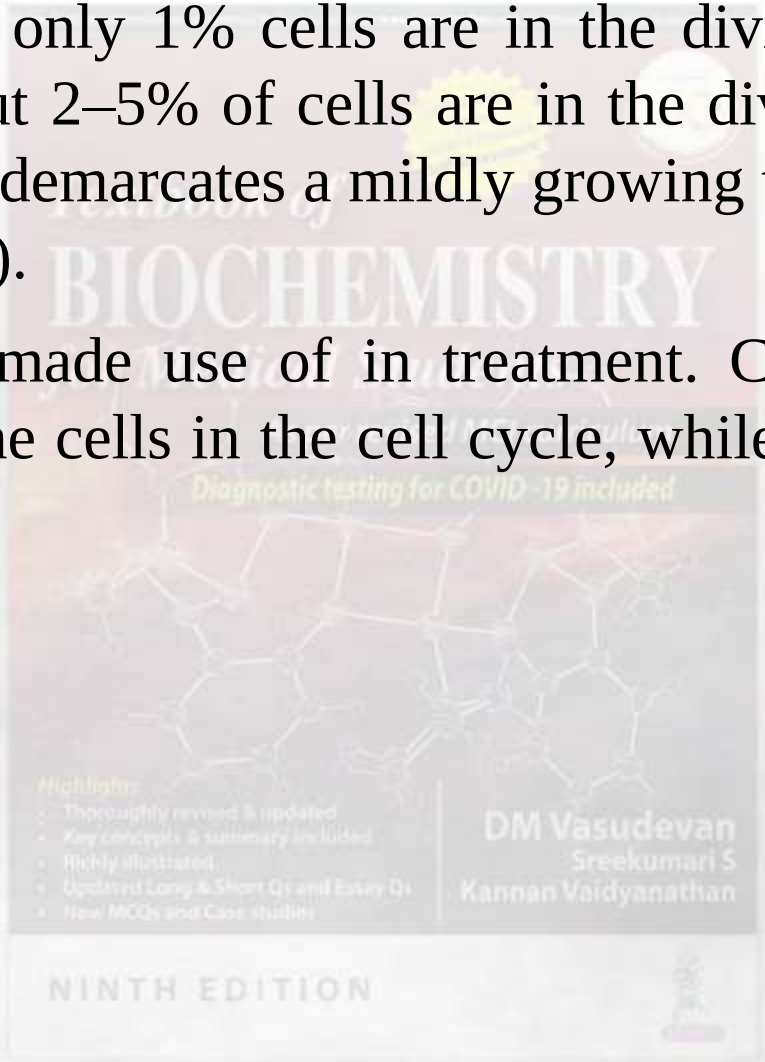


Differences between normal and cancer cells.

Tumor Kinetics

In a normal tissue, only 1% cells are in the dividing state while in cancer tissues, about 2–5% of cells are in the dividing phase of cell cycle. This number demarcates a mildly growing tumor (2%) from an aggressive one (5%).

This difference is made use of in treatment. Cytotoxic drugs and radiation will kill the cells in the cell cycle, while sparing the resting cells.



Doubling Time

Growth of a tumor mass depends on: (1) Cellular proliferation. (2) Cell death by apoptosis, lack of oxygen or nutrition and destruction by immunological mechanisms.

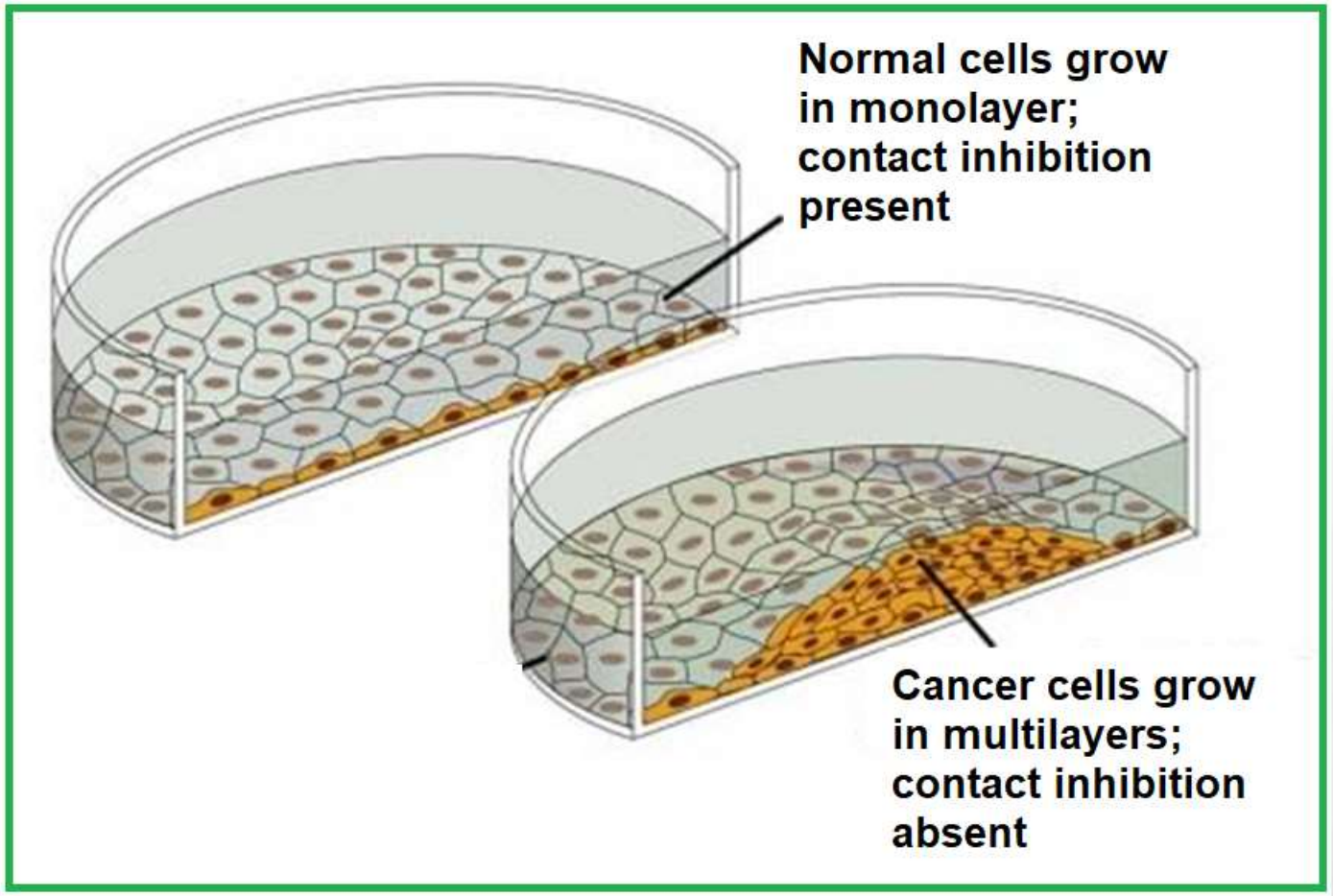
The doubling time is the time taken by a tumor to exactly double its mass, and is a constant for a particular growth over a long period. The tumor doubling time in human cancers varies widely between 10 days to 450 days, with a mean of about 100 days. Very rapidly growing tumors will need lesser days to double the volume. In the case of tumor with a doubling time of 100 days, the time taken for this growth to reach 1cm size from the initial mutated cell is about 8–10 years. Thus the tumor was present in the body for a considerable period before the clinical detection.

Malignant Transformation

When a normal cell has acquired malignant character, it is said to be transformed. In the cell culture, this is seen as alterations in morphology as well as changes in the alignment among the cells. Normal cells form a monolayer, while cancer cells show multi-layered appearance.

Contact Inhibition

It is a characteristic of normal cells. If a cut is made in the skin, the cells from both sides start to multiply. This multiplication is stopped when the cells come into contact. This is called contact inhibition. But in the case of cancer cells, tight junctions are rare, the property of contact inhibition is lost and adjacent cells continue to multiply to form multilayered or jumbled appearance.



Normal cells form a monolayer in culture (Left side). Same cells transformed in culture with multilayered appearance (Right side).

Metabolic Alterations in Cancer Cells

Generally cancer cells thrive on minimal enzymes. **Warburg's hypothesis** is that cancer cells favour glycolysis rather than oxidative phosphorylation. Another example is the deletion of asparagine synthetase in certain lymphomas.

Why Cancer Cells are Immortal?

One reason is that cancer cells have increased and persistent activity of telomerase, the enzyme that maintains the length of **telomeres** (end region of chromosomes).

Apoptosis

Programmed cell death is called apoptosis. Examples of apoptosis mediating genes *(suicidal genes)* are c-fos, p53, Rb; and so they in turn are oncosuppressor genes. By the same token, apoptosis protecting genes are cancer producing genes, e.g. bcl-2 and other oncogenes.

Cancer Cachexia

It is characterized by a reduction in body weight, resulting predominantly from the loss of skeletal muscle and adipose tissue. This is associated with anorexia, an inflammatory process, insulin resistance, and increased protein turnover. Cachexia leads to reduced cancer treatment tolerance and reduced quality and length of life. Mediators of cachexia include TNF-alpha, IL-6, IL-8 and proteolysis-inducing factor (PIF), produced by tumor cells and host immune cells. Laboratory findings are albumen less than 3 g/dL, pre-albumin value of less than 10 mg/dL, transferrin level less than 100 mg/dL, and elevated C–reactive protein.

Cancer Stem Cells (CSCs)

The CSCs have the ability to divide into new cancer cells. These are formed from differentiated adult cells and persist as a small percentage of the cancer cells. CSCs possess the ability to give rise to all cell types found in a particular cancer sample. CSCs may generate tumors through self-renewal and differentiation into multiple cell types. Such cells persist in tumors as a distinct population and cause relapse and metastasis. Conventional chemotherapies kill differentiated or differentiating cells, which form the bulk of the tumor. But CSCs, which will give rise to new tumor cells, could remain untouched and cause relapse.

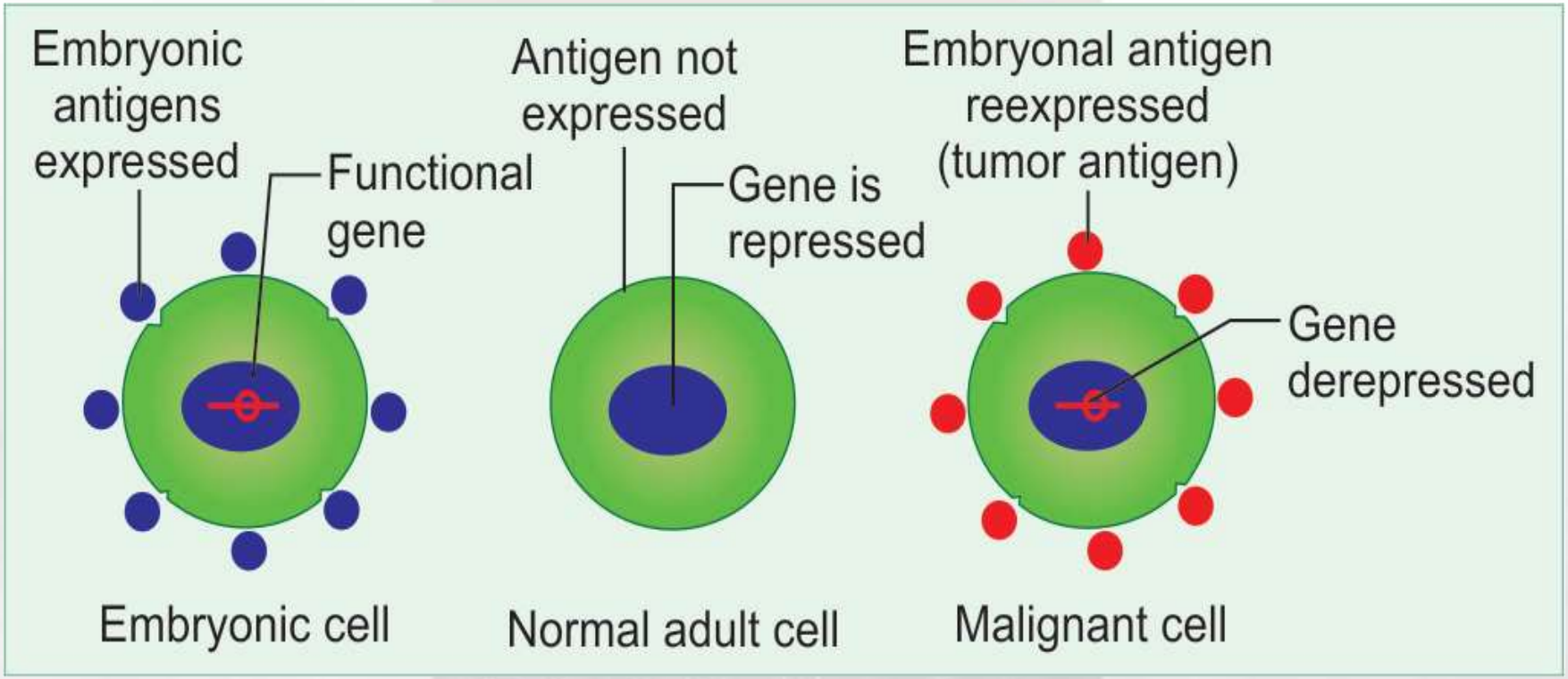
Tumor Immunology

All forms of treatment of cancer (surgery, radiotherapy and chemotherapy) leave some residual cancer cells in the body. These are annihilated by the body's immune mechanism. The effector arms of immunological mechanisms are (a) T cells, (b) NK cells, (c) antibody dependent complement mediated lysis, (d) antibody dependent cell mediated cytolysis (ADCC), and (e) macrophages. In the tumor bearing host, appreciable level of immunological reaction against the cancer is detected. Most of the human cancers show the emergence of oncofetal antigens. T cells are prevented from attacking tumors effectively.

Oncofetal Antigens

During the fetal life, a particular gene is active, and the product, a protein, is therefore produced in the cell. During the differentiation process, this gene is suppressed and therefore the protein is not present in adult cells. However, along with the malignant transformation, de-differentiation occurs, the gene is derepressed and the protein is again available in the cell. Such products are classified as oncofetal proteins.

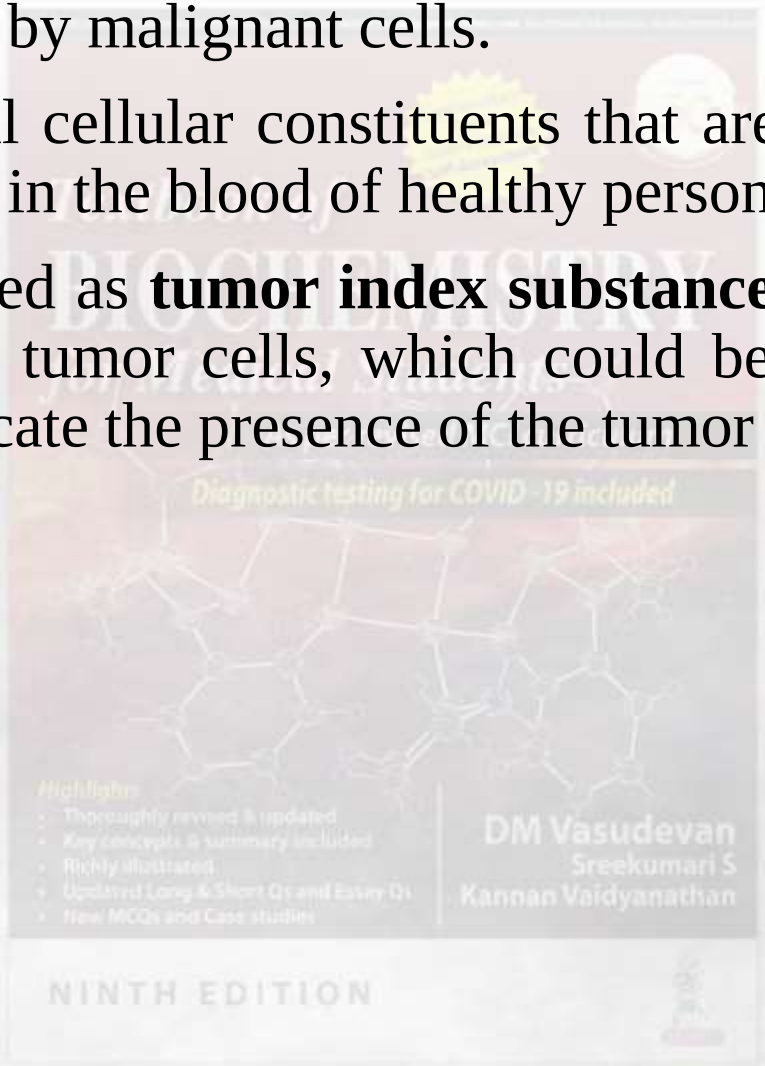
The best examples are the appearance of alpha-fetoprotein (AFP) in hepatomas and carcinoembryonic antigen (CEA) in colon cancers. They generally serve as tumor markers.



Oncofetal antigen.

Tumor Markers

- are overexpressed by malignant cells.
- are usually normal cellular constituents that are present at normal or very low levels in the blood of healthy persons.
- They are also called as **tumor index substances**. They are factors released from the tumor cells, which could be detected in blood and therefore indicate the presence of the tumor in the body.



Definition

"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"

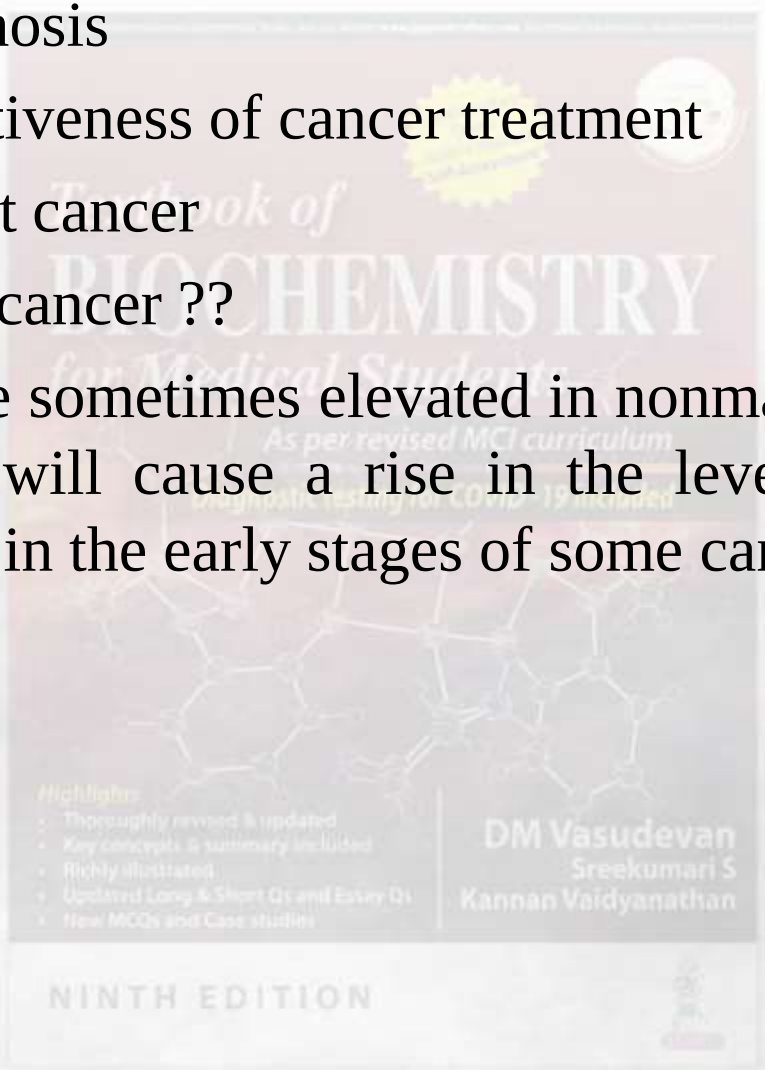
"A naturally occurring molecule, gene, or characteristic by which a particular pathological process, disease, etc. can be identified"

"A **biomarker** is a measurable indicator of the severity or presence of some disease state"

"A biomarker is anything that can be used as an indicator of a particular disease state"

Tumor markers are useful for

- Determining prognosis
- Determining effectiveness of cancer treatment
- Detecting recurrent cancer
- Early detection of cancer ??
- Tumor markers are sometimes elevated in nonmalignant conditions. Not every tumor will cause a rise in the level of its associated marker, especially in the early stages of some cancers.



Common tumor markers

Name	Serum level increased in
Oncofetal Products	
Alpha fetoprotein (AFP)	Hepatoma, germ cell cancers
Carcinoembryonic antigen (CEA)	Colorectal, gastrointestinal, and lung cancer
Carbohydrate Antigens	
CA-125	Ovarian cancer of epithelial origin
Tissue Antigens	
Tissue polypeptide antigen	General cancer load
Enzymes	
Alkaline phosphatase (ALP)	Bone secondaries
Placental type ALP (Regan)	Lung, seminoma
Prostatic acid phosphatase (PAP)	Prostate cancer
Prostate Specific Antigen (PSA)	Prostate cancer
Neuron Specific Enolase	Nervous system tumors

Common tumor markers, continued

Name	Serum level increased in
Hormones and their Metabolites	
Beta-HCG	Choriocarcinoma
Calcitonin	Medullary thyroid carcinoma
Big ACTH	Lung oat cell cancer
Vasoactive intestinal polypeptide (VIP)	Apudomas (Amine precursor uptake decarboxylation-omas)
Vanillyl mandelic acid (VMA)	Pheochromocytoma and neuroblastoma
Hydroxy indole acetic acid	Carcinoid syndrome
Tissue Catabolic Product	
Hydroxy proline	Bone metastasis

Common tumor markers, continued

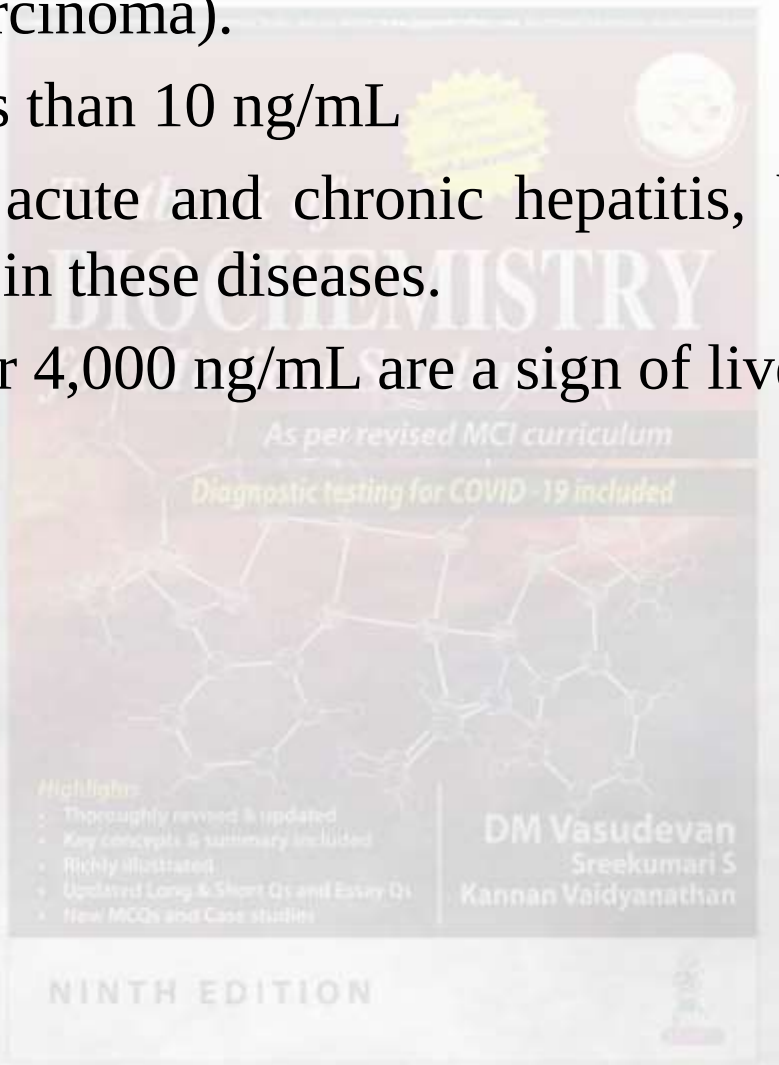
Name	Serum level increased in
Serum Proteins	
Immunoglobulins (Ig)	Multiple myeloma, macroglobulinemia
Bence-Jones proteins (in urine)	Multiple myeloma
Receptor Tumor markers	
Estrogen receptor (ER) and progesterone receptor (PR)	Carcinoma Breast ,Carcinoma Uterus
HER2/neu (erb2 or EGFR2)	Carcinoma breast

Selected molecular markers in cancers

Gene marker	Cancer detected
ALK gene rearrangements in tissues	Non-small cell lung cancer, anaplastic large cell lymphoma
BRCA1 and BRCA2 genes	Ovarian cancer
BCR-ABL fusion gene	Chronic myeloid leukemia, acute lymphoblasitc leukemia
BRAF V600 mutations	Melanoma, colorectal cancer
EGFR mutation analysis	Non-small cell lung cancer
Estrogen receptor (ER) and progesterone receptor (PR)	Breast cancer
HER2/neu gene in tissues	Breast cancer, gastric cancer
KRAS gene mutation analysis in tissues	Colorectal cancer and non-small cell lung cancer
Programmed death ligand 1 (PD-L1)	Non-small cell lung cancer

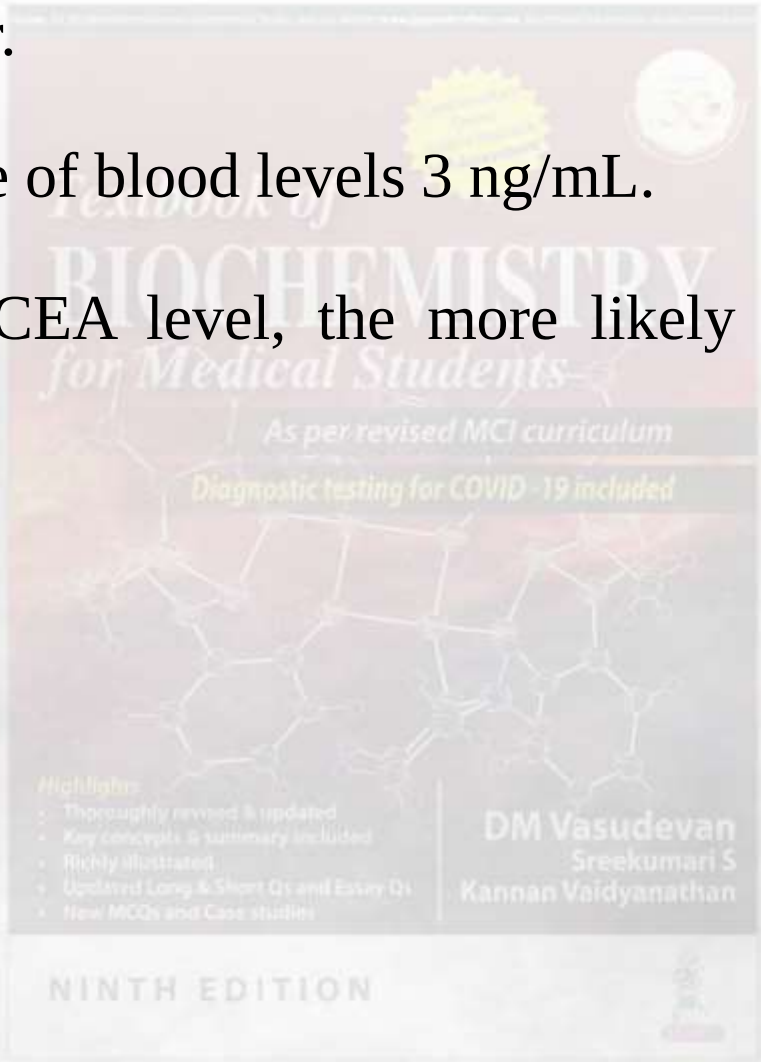
Alpha-fetoprotein (AFP)

- Hepatocellular carcinoma).
- Normal levels less than 10 ng/mL
- AFP elevated in acute and chronic hepatitis, but it seldom gets above 100 ng/mL in these diseases.
- AFP levels of over 4,000 ng/mL are a sign of liver cancer.



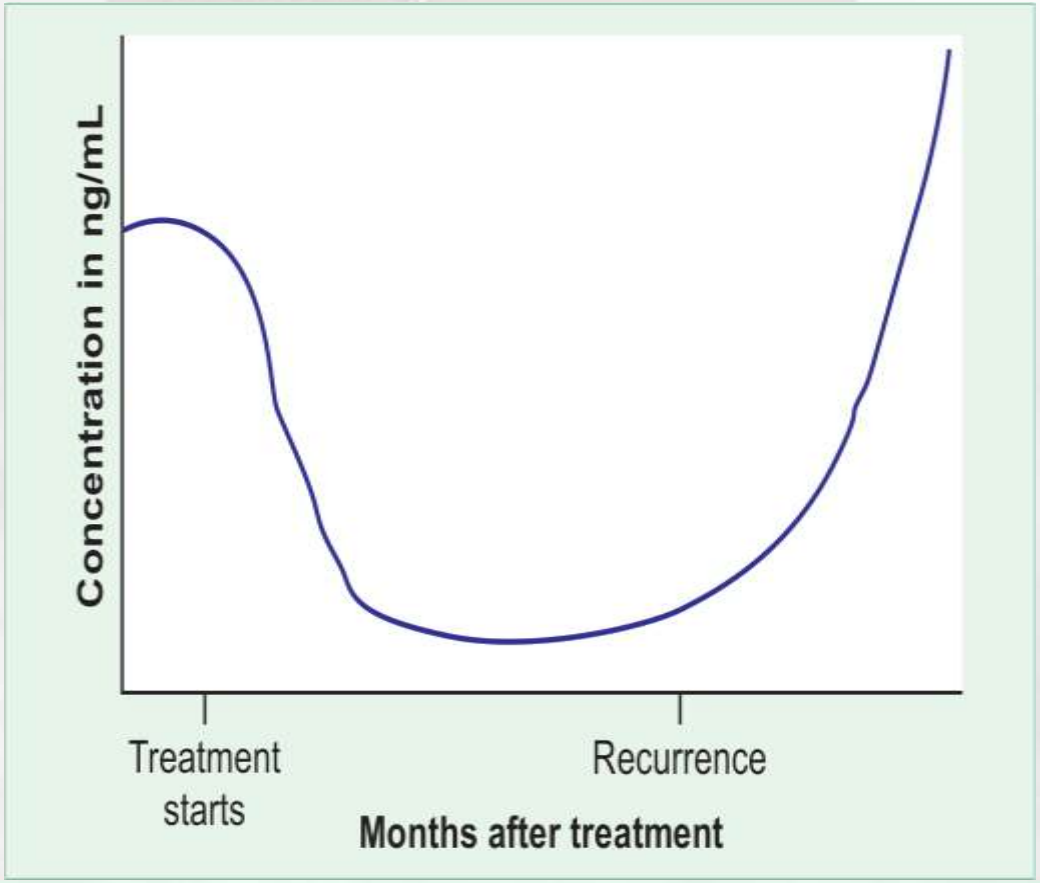
Carcinoembryonic antigen (CEA)

- Colorectal cancer.
- The normal range of blood levels 3 ng/mL.
- The higher the CEA level, the more likely that the cancer is advanced.



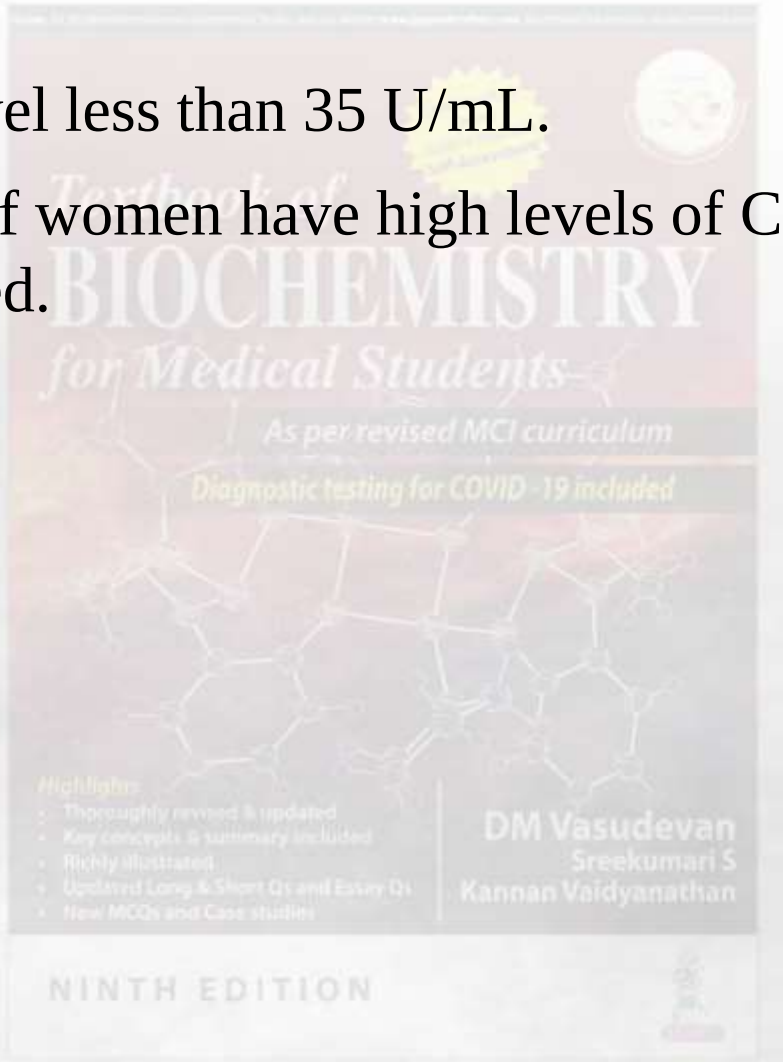
Human chorionic gonadotropin (Beta-HCG)

- Choriocarcinoma.
- Follow up
- recurrence.



CA - 125

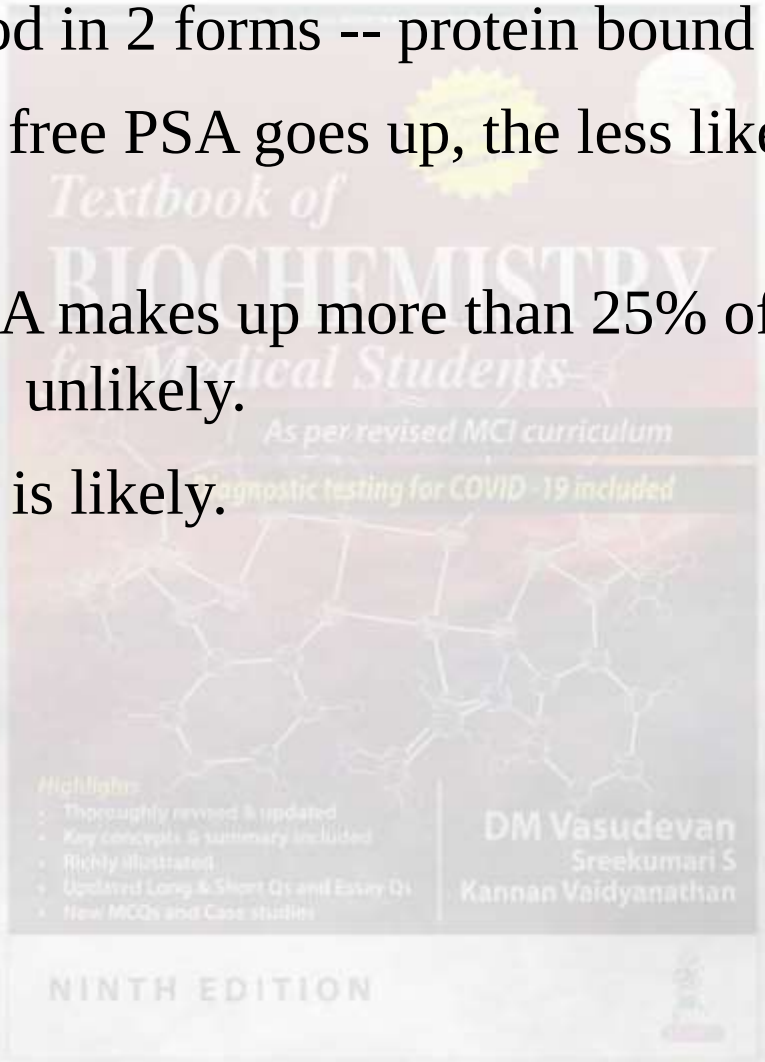
- Ovarian cancer.
- Normal blood level less than 35 U/mL.
- More than 90% of women have high levels of CA 125 when the cancer is advanced.



Prostate-specific antigen (PSA)

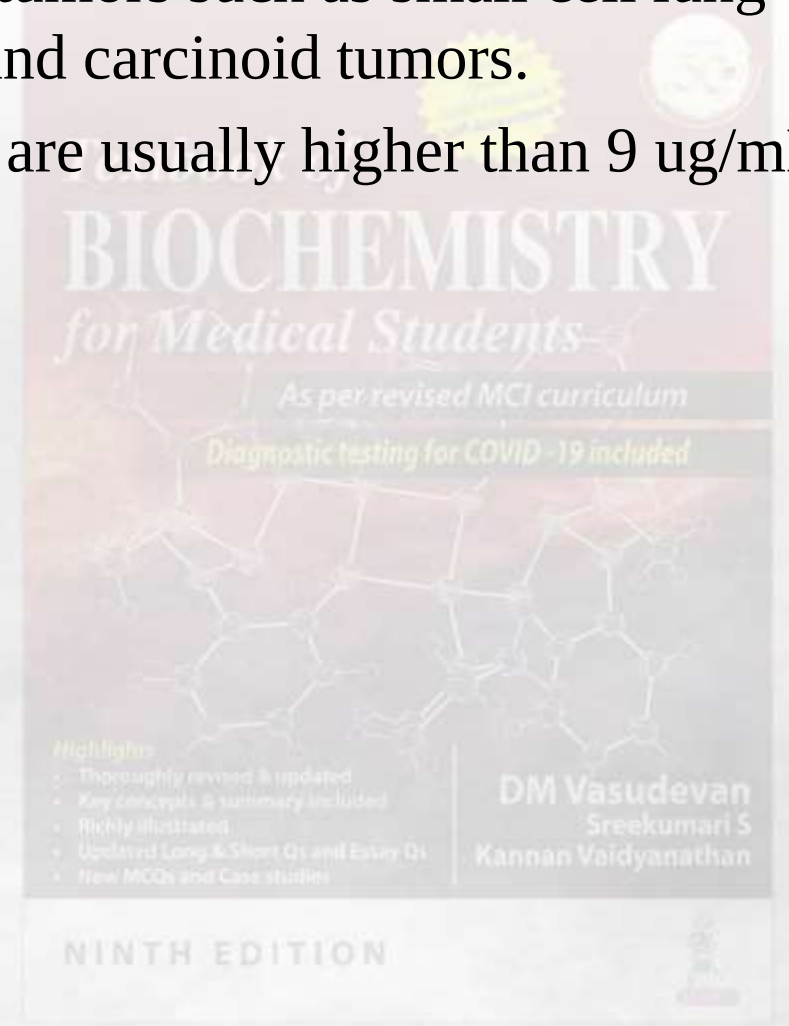
- Prostate cancer.
- Men with benign prostatic hyperplasia (BPH), often have higher levels.
- Normal below 4 ng/mL
- Levels greater than 10 ng/mL mean cancer is likely.
- The area between 4 and 10 is a gray zone (about a 1 in 4 chance of having prostate cancer).
- For PSA level, an increase from one year to the next may mean prostate cancer is more likely.
- This is called *PSA velocity*.
- PSA levels should be measured 3 times over a period of 18 months in order to get an accurate PSA velocity.

- PSA is in the blood in 2 forms -- protein bound and and free.
- As the amount of free PSA goes up, the less likely it is that there is prostate cancer.
- When the free PSA makes up more than 25% of the total PSA, prostate cancer is unlikely.
- Free 10%, cancer is likely.



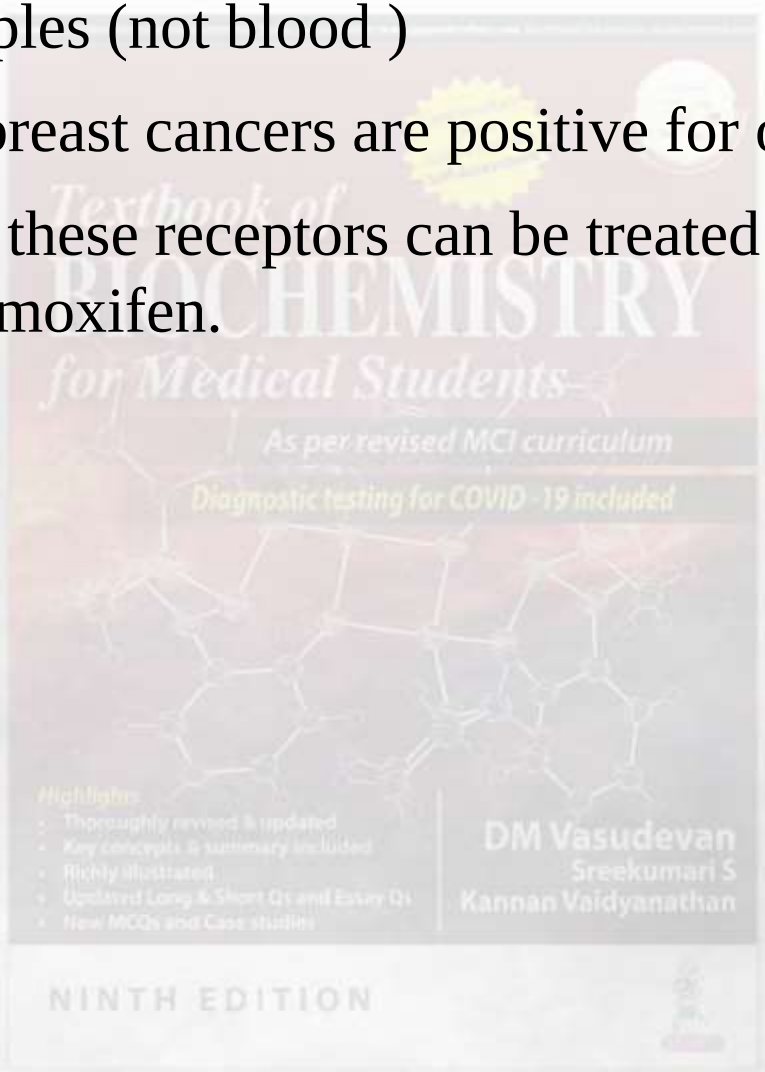
Neuron-specific enolase (NSE)

- Neuroendocrine tumors such as small cell lung cancer, neuroblastoma, and carcinoid tumors.
- Abnormal levels are usually higher than 9 ug/mL



Estrogen / Progesteron receptors

- Breast tumor samples (not blood)
- About 2 out of 3 breast cancers are positive for one of these markers.
- Cancers that have these receptors can be treated with hormone therapy such as tamoxifen.



HER2 (HER2/neu, or EGFR2)

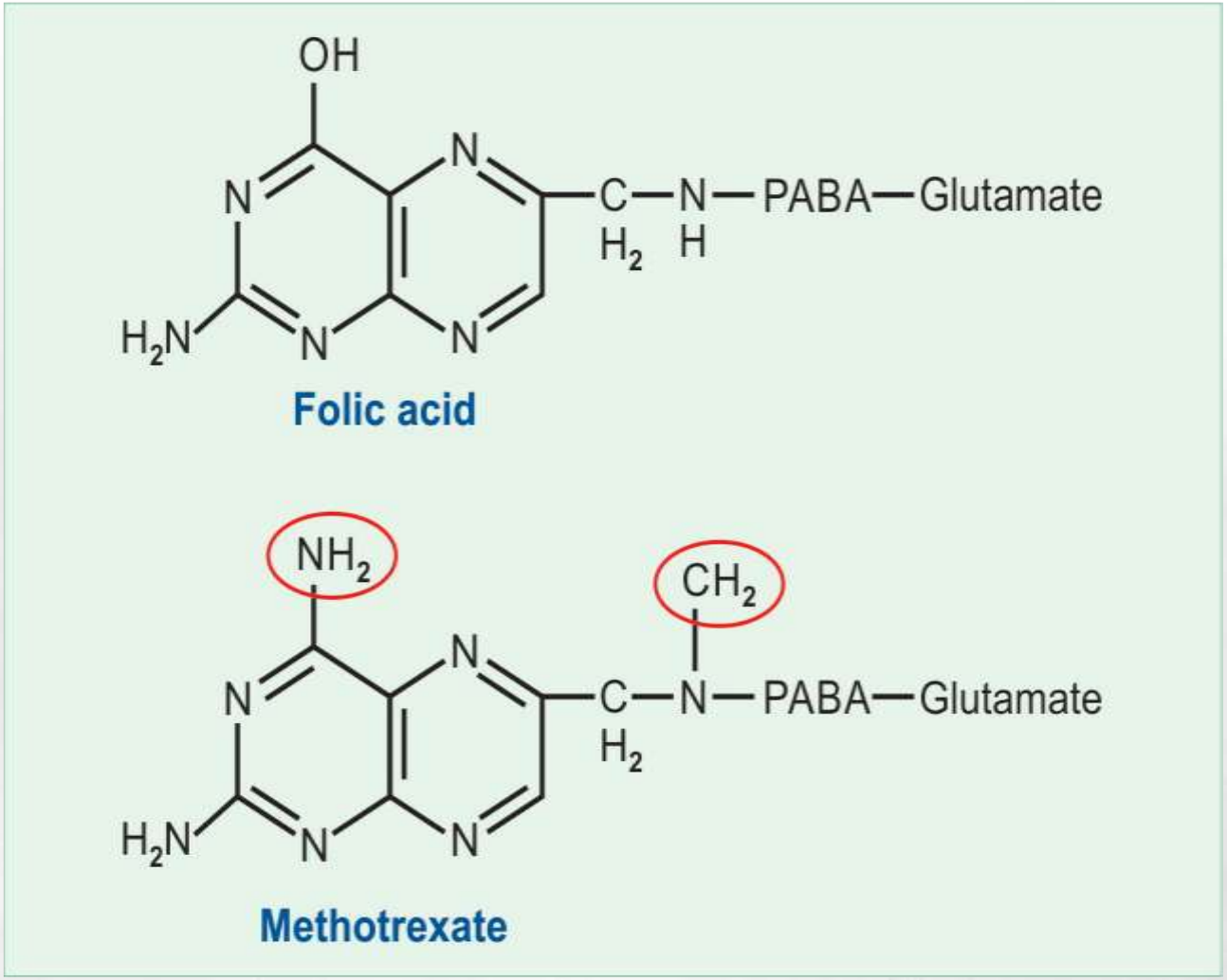
- It is a growth factor that tells breast cancer cells to grow.
- Testing a sample of the cancer tissue itself, not the blood.
- About 1 in 5 breast cancers test +ve
- These cancers tend to grow and spread more aggressively than other breast cancers.
- All newly diagnosed breast cancers should be tested for HER2.
- HER2-positive cancers will respond to trastuzumab (Herceptin®) and lapatinib (Tykerb®), which work against HER2 receptor on breast cancer cells.

Anticancer Drugs

Surgery and radiotherapy are most effective to reduce the initial tumor load. These are the prime modalities of treatment in solid tumors.

Chemotherapy is the sheet anchor of therapy in leukemias, lymphomas, choriocarcinoma and other widely disseminated malignancies. The effectiveness of cytotoxic drugs is directly proportional to the doubling time of the tumors, and is inversely proportional to the number of cancer cells. Cytotoxic drugs affect all the cells which are in the dividing phase.

The rapidly dividing normal cells (gastrointestinal tract, hematopoietic system, hair follicles, gonads) are also affected by chemotherapeutic drugs, leading to toxicity.



Red circles denote the structural alterations in methotrexate.

Common anticancer drugs

Name	Type	Mode of action
Methotrexate	Folic acid analog	Competitive inhibitor of dihydrofolate reductase. THFA is required for nucleotide synthesis
6-Mercaptopurine	Purine analogue	Inhibits the conversion of IMP to AMP
6-thioguanine	Purine analogue	Inhibits synthesis of purine nucleotides
5-fluoro uracil	Pyrimidine analogue	Inhibits thymidylate synthase
Cyclophosphamide	Alkylating agent	Cross linking of bases of DNA; inhibition of strand separation
Mitomycin C	Antibiotic	Cross bridges are formed between DNA base pairs

Common anticancer drugs, continued

Name	Type	Mode of action
Actinomycin D	Antibiotic	Intercalates with guanine bases of DNA; prevents transcription
Vincristine and Vinblastine	Alkaloids from Vinca rosea	Interferes with assembly of cytoskeleton and inhibits Stathmokinesis (spindle movement)
Adriamycin	Anthracyclins	Topo-isomerase mediated breaks in DNA
Etoposide	Podophyllo-toxin	Stabilises topo-isomerase-II-DNA cleavage complexes
Cis-platin	Platinum compound	Forms intrastrand DNA adducts
Taxanes	Apoptosis inducer	Inhibits mitotic spindle formation; used in carcinoma breast

Monoclonal antibodies used as anticancer agents

Name	Target	Used against the cancer
Alemtuzumab	CD52 on B cells	B cell CLL
Bevacizumab	VEGF	Colorectal, solid tumors of kidney
Blinatumomab	CD19	B cell ALL
Cetuximab	KRas	Colorectal, head and neck
Daratumumab	CD38	Multiple myeloma
Dinutuximab	Disialoganglioside GD2	Pediatric neuroblastoma
Elotuzumab	SLAMF7	Multiple myeloma
Panitumumab	EGFR	Colorectal cancer
Imatinib	Tyrosine kinase	CML
Ipilimumab	CTLA-4	Metastatic melanoma

Monoclonal antibodies used as anticancer agents

Name	Target	Used against the cancer
Lapatinib	Tyrosine kinase	Carcinoma breast
Nivolumab	PD-1	Metastatic melanoma, non-small cell lung carcinoma
Ofatumumab	CD20	CLL
Olaratumab	PDGFRA	Soft tissue sarcome
Panitumumab	EGFR	Colorectal cancer
Pembrolizumab	PD-1	Metastatic melanoma
Rituximab	CD20	NHL, CLL, B cell leukemia
Sorafenib	VEGF	Renal cell cancer, hepatocellular carcinoma
Trastuzumab (Herceptin)	HER-2/neu (EGFR2, Erb-B2)	Breast cancer

Abbreviations used in the previous slides

ALL = acute lymphoblastic leukemia,
CLL = chronic lymphocytic leukemia,
CML = chronic myeloid leukemia,
EGFR = epithelial growth factor receptor,
NHL = non-Hodgkin's lymphoma,
PDGFRA = platelet derived growth factor receptor alpha,
VEGF = vascular endothelial growth factor.